ORIGINAL RESEARCH

Low Circulating Musclin is Associated With Adverse Prognosis in Patients Undergoing Transcatheter Aortic Valve Implantation at Low-Intermediate Risk

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BACKGROUND: Musclin is an activity-stimulated and cardioprotective myokine that attenuates pathological cardiac remodeling. Musclin deficiency, in turn, results in reduced physical endurance. The aim of this study was to assess the prognostic value of circulating musclin as a novel, putative biomarker to identify patients undergoing transcatheter aortic valve implantation (TAVI) who are at a higher risk of death.

METHODS AND RESULTS: In this study, we measured systemic musclin levels in 368 patients undergoing TAVI who were at low to intermediate clinical risk (median EuroSCORE [European System for Cardiac Operative Risk Evaluation] II: 3.5; quartile 1–quartile, 2.2%–5.3%), whereby 209 (56.8%) patients were at low and 159 (43.2%) were at intermediate risk. Median preprocedural musclin levels were 2.7 ng/mL (quartile 1–quartile 3, 1.5–4.6 ng/mL). Musclin levels were dichotomized in low (<2.862 ng/mL, n=199 [54.1%]) or high (≥2.862 ng/mL, n=169 [45.9%]) groups using cutoff values determined by classification and regression tree analysis. The primary end point was 1-year overall survival. Patients with low circulating musclin levels exhibited a significantly higher prevalence of frailty, low albumin values, hypertension, and history of stroke as well as higher N-terminal pro-B-type natriuretic peptide. Low musclin levels significantly predicted risk of death in univariable (hazard ratio, 1.81; 95% CI, 1.00–3.53 [P=0.049]) and multivariable (adjusted hazard ratio, 2.45; 95% CI, 1.06–5.69 [P=0.037]) Cox regression analyses. Additionally, low musclin levels in combination with conventional EuroSCORE II suggested improved risk stratification in patients undergoing TAVI who were at low to intermediate clinical risk into subgroups with reduced 1-year survival rates by log-rank test (P for trend=0.003).

CONCLUSIONS: Circulating musclin is an independent predictor of 1-year overall survival in patients undergoing TAVI. Combined with EuroSCORE II, circulating musclin might help to improve prediction of mortality in patients undergoing TAVI who are at low to intermediate clinical risk.

Key Words: aortic valve stenosis ■ biomarker ■ musclin ■ TAVI

Transcatheter aortic valve implantation (TAVI) has rapidly emerged as a less invasive alternative to surgical aortic valve replacement in patients with severe aortic valve stenosis (AS) who are at high operative risk.[1] Conventional risk scores (such as EuroSCORE [European System for Cardiac Operative Risk Evaluation] II or Society of Thoracic Surgeons (STS) predicted risk of mortality) have been widely used by "Heart Teams" for risk stratification to assign patients with AS to either TAVI or surgical aortic valve replacement based on the estimated perioperative and long-term risk.[2–4] However, indications for TAVI have recently been expanded across the entire risk spectrum, including patients with AS at low to intermediate clinical risk.[4–6] While conventional risk scores have been applied in TAVI populations, risk discrimination is insufficient to

CLINICAL PERSPECTIVE

What Is New?

- Low levels of an activity-stimulated and cardioprotective myokine (called musclin) independently predict increased risk of death in patients undergoing transcatheter aortic valve implantation.
- Patients with reduced circulating musclin levels had a significantly higher prevalence of frailty, history of stroke, lower albumin values, and higher N-terminal pro-B-type natriuretic peptide level, indicating impaired exercise capacity insufficiently mapped by conventional clinical risk scores.
- Assessment of musclin level in combination with conventional risk scores suggested improved risk stratification in patients undergoing transcatheter aortic valve implantation into subgroups with reduced 1-year survival rates.

What Are the Clinical Implications?

- Measurement of musclin as a putative biomarker might improve outcome prediction in the expanding group of patients undergoing transcatheter aortic valve implantation who have low-intermediate clinical risk, in whom appropriate risk stratification and biomarker assessment is still insufficient.

Non-standard Abbreviations and Acronyms

AR	aortic regurgitation
AS	aortic valve stenosis
CART	classification and regression tree
EuroSCORE	European System for Cardiac Operative Risk Evaluation
STS	Society of Thoracic Surgeons
TAVI	transcatheter aortic valve implantation

identify those patients at low or intermediate clinical risk who will benefit from TAVI.[7,8] Thus, novel parameters such as circulating biomarkers are needed to improve clinical risk stratification in patients undergoing TAVI by integrating untargeted health conditions that may contribute to adverse outcomes beyond the expanded low to intermediate clinical risk classification according to clinical characteristics determined by EuroSCORE II or STS predicted risk of mortality.

Musclin (also known as osteocrin) may serve as a novel putative biomarker, which might integrate untargeted health conditions having been identified as a skeletal muscle–derived, activity-stimulated, and cardioprotective myokine that enhances physical endurance.[9–11] Interestingly, musclin-treated mice exhibit improved survival and ameliorated myocardial hypertrophy by reducing cardiac inflammation.[11] In turn, musclin deficiency is associated with reduced physical endurance, impaired bone growth, and impaired skeletal muscle function during cancer cachexia.[12–15] Thus, circulating musclin levels may serve as a quantitative parameter reflecting overall physical capacity of individual patients. Therefore, in this pilot study, we analyzed the prognostic value of circulating musclin levels in patients with AS undergoing TAVI who have low to intermediate risk.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Cohort

In this prospective, observational study, a total of 368 consecutive patients at low to intermediate clinical risk with available peripheral blood samples undergoing TAVI for severe AS at the University Hospital of the Goethe University Frankfurt (Germany) between February 2017 and December 2019 were studied. In this all-comers study, patients with isolated or combined severe aortic regurgitation (AR) and patients requiring a valve-in-valve procedure were also included. Patients were stratified into risk categories based on EuroSCORE II with an estimated risk of mortality <4% comprising the low-risk group and between 4% and 10% defining the intermediate-risk group, respectively.[4,16–18] Nine patients with follow-up <30 days have been excluded in order to remove mortality related to periprocedural complications. All patients provided written informed consent. The ethics review board approved the protocol, and the study complies with the Declaration of Helsinki. Clinical data, echocardiographic findings, and laboratory data were prospectively collected as part of clinical routine. The single clinical end point was overall survival.

Laboratory Measurements

Peripheral venous blood samples were obtained at admission for standard baseline laboratory parameters and immediately before starting the TAVI procedure for musclin level assessment. Serum high-sensitivity troponin T and NT-proBNP (N-terminal pro-B-type natriuretic peptide) were only available in 249 and 328 of 368 patients, respectively, before TAVI because of missing test conduction during clinical routine.

Measurement of Circulating Musclin

Serum biomarker levels were analyzed at our institution`s core facility. Circulating musclin (also known as osteocrin) was measured with the human Osteocrin ELISA kit (Cusabio, CSB-E12021H; with a minimal detection dose of 0.0078 ng/mL) according to the manufacturer´s instructions. The assay is a solid-phase ELISA that employs the quantitative sandwich enzyme immunoassay technique. Blood samples were stored at −80 °C.

Statistical Analysis

Continuous variables are presented as median (interquartile range [IQR]) unless otherwise noted. Categorical variables were compared by the χ^2 test or Fisher exact test as appropriate. To provide a simple, exploratory analysis, we performed survival classification and regression tree (CART) analysis using the primary end point as an outcome variable, with preprocedural musclin levels as an independent variable.[19–22] The purpose was to identify the cutoff value of musclin for the risk stratification of the primary end point.[23] Next, we divided the study population into 2 groups based on this analysis. Patients with musclin levels lower than the cutoff value were defined as having low musclin, whereas those with musclin levels greater than the cutoff value were defined as having high musclin. Next, the Kaplan–Meier analysis was used to estimate cumulative survival at 1-year according to the cutoff (musclin level <2.862 or ≥2.862 ng/mL) determined by CART analysis. For survival analyses, all continuous parameters were dichotomized for unadjusted Kaplan–Meier analysis and to keep the Cox model simple. Since most of the variables showed skewed distributions, the upper quartile was chosen as a limit for high values. Differences were detected by log-rank test. Multivariable Cox proportional regression analysis was performed to account for the potential effect of confounding variables. We evaluated the impact of lower musclin on 1-year survival compared with higher circulating musclin levels using univariable and multiple Cox regression models. All preprocedural prognostic factors that were significant in the log-rank test as well as variables based on clinical relevance or that yielded a P value <0.200 in the univariable analysis were included in a multivariable Cox regression analysis (model 1 with an effect size of 0.103). In addition, diabetes, insulin therapy, and body mass index were included in a second multiple Cox regression analysis (model 2 with an effect size of 0.109), as musclin has been implicated as a putative target for obesity and associated diseases.[14,24] To assess the predictive capacity of musclin in terms of 1-year cumulative survival, the following variables were included as possible confounders: previous percutaneous coronary intervention,[25,26] EuroSCORE II,[8] left ventricular dysfunction,[27] frailty,[28,29]

atrial fibrillation,[30] NTproBNP,[31] high-sensitivity troponin T,[32] absence of preexisting AR,[33,34] chronic obstructive pulmonary disease,[35] arterial hypertension, peripheral artery disease,[36] albumin level,[37] age, sex,[38,39] body mass index,[40,41] diabetes,[24,42] and insulin therapy[43]. For exploratory purposes, we further estimated improved risk stratification by log-rank test for linear trend to compare survival curves based on dichotomized circulating musclin and clinical risk: (1) higher musclin level (≥2.862 ng/mL) and low clinical risk (EuroSCORE II <4%); (2) higher musclin level (≥2.862 ng/mL) and intermediate EuroSCORE II; (3) lower musclin level (<2.862 ng/mL) and low EuroSCORE II; and (4) lower musclin level (<2.862 ng/mL) and intermediate EuroSCORE II. P values ≤0.05 were significant, without adjusting for multiple comparisons because of the low number of patients in the subgroups. Statistical analysis was performed with SPSS statistical software version 27.0 (IBM).

RESULTS

Patient Characteristics

We analyzed musclin serum levels in 368 patients with AS at low to intermediate clinical risk undergoing TAVI. During a median follow-up of 502 days (95% CI, 452.9–551.0 days), the estimated 1-year overall survival rate in the total study cohort was 82%. The baseline characteristics of the study population are summarized in Table 1. The median age of the total population was 82.2 years, and 43.5% of the patients were women. Hypertension, diabetes, and COPD were found in 84.5%, 30.2%, and 18.8% of all patients, respectively. Most of the patients had New York Heart Association class III/IV heart failure (75.0%), and 44.8% of the patients had chronic atrial fibrillation. Approximately three quarters of the study patients had coronary artery disease, with 8.4% experiencing previous cardiac surgery. The mean pressure gradient across the aortic valve was 42.0 mm Hg. The median EuroSCORE II was 3.5% (quartile 1 [Q1]–quartile 3 [Q3], 2.2%–5.3%), whereas STS score was 3.2 (Q1–Q3, 2.3–4.8). Median pre-TAVI NT-proBNP levels and high-sensitivity troponin T levels were 2077 pg/mL (Q1–Q3, 1293.5–4160 pg/mL) and 22 pg/mL (Q1–Q3, 14–34 pg/mL), respectively, whereas the median preprocedural musclin value was 2.7 ng/mL (Q1–Q3, 1.5–4.6 ng/mL). The overall 1-year mortality rate was 14.1%, with 52 patients dying over this period.

Association Between Systemic Musclin Level and Baseline Clinical Characteristics

Next, we examined whether circulating musclin levels might be associated with clinical risk factors according to the cutoff of circulating musclin determined by CART

Table 1. Cardiovascular baseline characteristics of the TAVI study cohort (low vs high musclin levels)

	Total	Low musclin (<2.862 ng/mL)	High musclin (≥2.862 ng/mL)	
	(N=368)	(n=199)	(n=169)	P value
Age, y				0.053
Median	82.2	83.0	81.5	
IQR	78.9–85.3	78.9–86.1	78.9–84.7	
Sex				0.399
Men, n (%)	208 (56.5)	108 (54.3)	100 (59.2)	
Women, n (%)	160 (43.5)	91 (45.7)	69 (40.8)	
Height, m				0.478
Median	1.7	1.7	1.7	
IQR	1.6–1.8	1.6–1.74	1.6–1.76	
Weight, kg				0.179
Median	75.0	75.0	76.0	
Range	67.0–87.0	66.0–86.0	68.0–90.0	
BMI, kg/m^2				0.387
Median	26.3	26.2	26.4	
Range	23.9–29.8	23.4–29.6	24.5–30.1	
BMI, quartile 4 (n [%])	92 (25.0)	48 (24.1)	44 (26.0)	0.718
Hypertension, n (%)	311 (84.5)	179 (89.9)	132 (78.1)	0.002*
Diabetes, n (%)	111 (30.2)	58 (29.1)	53 (31.4)	0.650
Insulin therapy, n (%)	27 (7.3)	16 (8.0)	11 (6.5)	0.689
COPD, n (%)	69 (18.8)	41 (20.6)	28 (16.6)	0.350
CAD, n (%)	234 (63.6)	124 (62.3)	110 (65.1)	0.589
Peripheral artery disease, n (%)	42 (11.4)	17 (8.5)	25 (14.8)	0.071
Cerebrovascular arterial disease, n (%)	53 (14.4)	26 (13.1)	27 (16.0)	0.459
Atrial fibrilliation, n (%)	165 (44.8)	98 (49.2)	67 (39.6)	0.074
Previous MI, n (%)	58 (15.8)	28 (14.1)	30 (17.8)	0.389
Previous stroke, n (%)	38 (10.3)	28 (14.1)	10 (5.9)	0.015*
Previous PCI, n (%)	148 (40.2)	77 (38.7)	71 (42.0)	0.524
Previous cardiac surgery, n (%)	31 (8.4)	14 (7.0)	17 (10.1)	0.348
P mean (aortic valve), mm Hg				0.115
Median	42.0	44.0	42.0	
IQR	33.0–51.0	35.0–52.0	31.0–49.0	
Absence of preexisting AR, n (%)	89 (24.9)	45 (23.6)	44 (26.5)	0.542
NYHA class, n (%)				0.117
NYHA I/II	92 (25.0)	43 (21.6)	49 (29.0)	
NYHA III/IV	276 (75.0)	156 (78.4)	120 (71.0)	
Frailty, n (%)	170 (46.2)	103 (51.8)	67 (39.6)	0.021*
EuroSCORE II				0.335
Median	3.5	3.7	3.3	
IQR	2.2–5.3	2.3–5.3	2.1–5.3	
STS score, n (%)				0.662
Median	3.2	3.4	3.0	
IQR	2.3–4.8	2.3–4.6	2.3–5.2	
eGFR, mL/min				0.368
Median	59.5	59.1	59.9	

(Continued)

Table 1. Continued

	Total	Low musclin (<2.862 ng/mL)	High musclin (≥2.862 ng/mL)	
	(N=368)	(n=199)	(n=169)	P value
IQR	45.4–74.3	43.6–73.1	47.1–74.5	
Serum creatinine, mg/dL				0.752
Median	1.1	1.1	1.1	
IQR	0.9–1.4	0.9–1.4	0.9–1.3	
Serum creatinine, quartile 4 (n [%])	84 (22.8)	49 (24.6)	35 (20.7)	0.386
Low albumin (<3.5 g/L), n (%)	18 (5.1)	9 (4.7)	9 (5.7)	0.809
Musclin level, ng/mL				0.000*
Median	2.7	1.6	5.0	
IQR	1.5–4.6	1.0–2.1	3.6–7.4	
Albumin level, g/L				0.025*
Median	4.3	4.2	4.4	
IQR	3.9–4.5	3.9–4.5	4.0–4.6	
NT-proBNP, pg/mL				0.029*
Median	2077.0	2203.0	1935.0	
IQR	1293.5–4160.0	1430.3–5157.3	1153.5–3543.3	
NT-proBNP, quartile 4 (n [%])	62 (24.9)	39 (29.5)	23 (19.7)	0.117
High-sensitivity troponin, pg/mL				0.739
Median	22.0	21.5	22.5	
IQR	14.0–34.0	5.0–349.0	4.0–670.0	
High-sensitivity troponin, quartile 4 (n [%])	80 (24.4)	44 (25.0)	36 (23.7)	0.798
Ejection fraction, n (%)				0.805
Median	60.0	60.0	60.0	
IQR	50.0–60.0	20.0–80.0	15.0–74.0	
LVEF catecory, n (%)				0.664
Preserved LVEF	250 (67.9)	138 (69.3)	66.3	
Mildly reduced LVEF	48 (13.0)	23 (11.6)	14.8	
Moderately reduced LVEF	54 (14.7)	28 (14.1)	15.4	
Severely reduced LVEF	16 (4.3)	10 (5.0)	6 (3.6)	
LV dysfunction, n (%)	53 (14.4)	30 (15.1)	23 (13.6)	0.690
EuroSCORE II, n (%)				0.529
Low risk (<4%)	209 (56.8)	110 (55.3)	58.6	
Intermediate risk (≥4%)	159 (43.2)	89 (44.7)	70 (41.4)	
STS score, n (%)				0.913
Low risk (<4%)	239 (64.9)	130 (65.3)	109 (64.5)	
Intermediate risk (≥4%)	129 (35.1)	69 (34.7)	60 (35.5)	

AR indicates BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; and TAVI, transcatheter aortic valve implantation.

*indicates statistical significance (P value<0.05).

analysis (Figure – Panel A). In this study cohort, lower musclin levels (<2.862 ng/mL) in patients with AS undergoing TAVI were associated with a higher percentage of arterial hypertension (P=0.002), frailty (P=0.021), lower albumin levels (P=0.025) and higher NT-proBNP levels (P=0.029), as well as a higher frequency of previous stroke (P=0.015). In addition, there was a trend towards a higher frequency of chronic atrial fibrillation (P=0.074) and a slightly increased age (P=0.053) in patients with AS and lower musclin levels (Table 1). Of note, there

were no relevant differences in sex, body mass index, diabetes, insulin therapy, or EuroSCORE II (P=0.529) and STS-predicted risk of mortality (P=0.913).

Prognostic Value of Musclin for Patients Undergoing TAVI at Low to Intermediate Risk

To examine the impact of musclin on 1-year overall survival in patients undergoing TAVI who were at low to intermediate risk, we performed Kaplan–Meier analysis with log-rank tests according to the cutoff of circulating musclin determined by CART analysis (Figure – Panel B). Importantly, lower musclin levels (<2.862 ng/mL) were significantly associated with poor clinical outcome after TAVI (P=0.044). Because patients with lower musclin levels showed a higher frequency of hypertension, frailty, previous stroke, and higher NT-proBNP levels, we separately analyzed the Kaplan–Meier survival curves of these variables. In this TAVI cohort, frailty (P=0.001), COPD (P=0.034), absence of preexisting AR (P=0.009), and a higher EuroSCORE II (P=0.007) were variables individually associated with reduced 1-year survival in patients undergoing TAVI. While low versus intermediate EuroSCORE II exhibit an early effect on survival, survival curves based on musclin level indicate a late effect on survival (Figure – Panel B and C).

Next, we performed univariable Cox regression analysis to confirm the value of circulating musclin as a predictor for adverse outcomes in patients at low to intermediate clinical risk undergoing TAVI. Indeed, lower systemic musclin levels showed a hazard ratio (HR) of 1.81 (95% CI, 1.00–3.53; P=0.049) suggesting significance for predicting 1-year mortality (Table 2). In addition, univariable Cox regression analysis indicated that frailty (HR, 2.59; CI, 1.44–4.67 [P=0.002]), COPD (HR, 1.88, CI, 1.03–3.43 [P=0.038]), absence of preexisting AR (HR, 2.10; CI, 1.18–3.68 [P=0.011]), and a higher EuroSCORE II (HR, 2.10; CI, 1.20–3.62 [P=0.010]) were also independent predictors of adverse outcomes after TAVI (Table 2).

Multivariable Cox proportional regression analysis was performed to account for the potential effect of confounding variables (Table 2). After multivariable adjustment, the association of lower musclin levels with the primary end point remained statistically significant (HR, 2.45; CI, 1.06–5.69 [P=0.037]). Moreover, our analysis revealed that frailty (HR, 3.25; CI, 1.35–7.79 [P=0.008]) and preprocedural absence of AR (HR, 2.77; CI, 1.13–6.77 [P=0.026]) were other independent risk factors for reduced 1-year survival, while hypertension (HR, 0.38; CI, 0.15–0.99 [P=0.047]) and previous percutaneous coronary intervention (HR, 0.38; CI, 0.17–0.85 [P=0.018]) were associated with improved survival. Importantly, age, sex, diabetes, insulin therapy, and
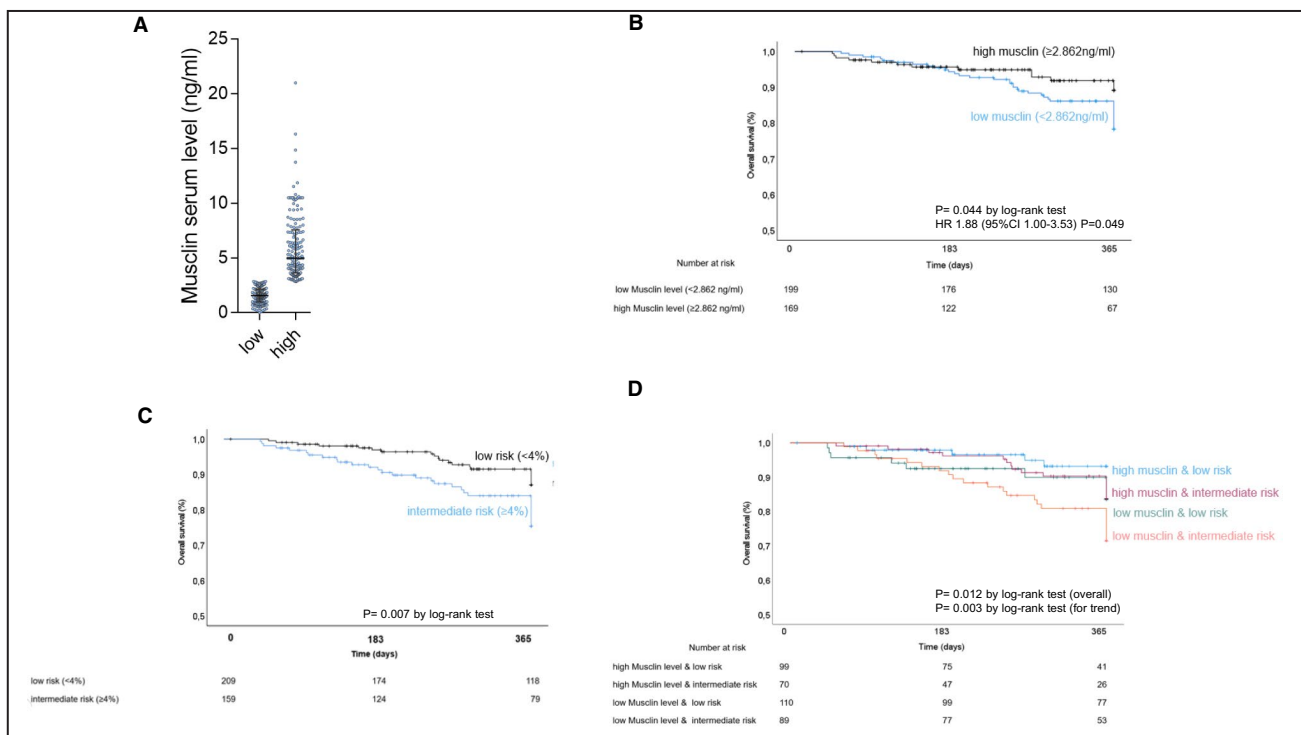
Figure. **Musclin predicts outcome in patients undergoing transcatheter aortic valve implantation.**
A, Distribution of musclin levels within the study cohort with low (<2.862 ng/mL) and high (≥2.862 ng/mL) circulating musclin determined by classification and regression tree analysis. **B through D**, Survival curves based on (**B**) circulating musclin, (**C**) European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, and (**D**) the combination of systemic musclin and EuroSCORE II (low risk <4% and intermediate risk ≥4%). HR indicates hazard ratio.

Table 2.   Results of survival analyses in patients undergoing TAVI (univariable and multivariable Cox regression analysis)

	Total TAVI cohort (N=368)					
	Crude HR		Adjusted HR		Adjusted HR	
	95% CI	P value	Model 1	P value	Model 2	P value
Musclin level (low)	1.81 (1.00–3.53)	0.049*	2.34 (1.01–5.42)	0.047*	2.45 (1.06–5.69)	0.037*
Frailty	2.59 (1.44–4.67)	0.002*	2.59 (1.12–5.81)	0.021*	3.25 (1.35–7.79)	0.008*
EuroSCORE II (≥4%)	2.10 (1.20–3.62)	0.010*	1.47 (0.70–3.10)	0.312	1.46 (0.65–3.30)	0.364
COPD	1.88 (1.03–3.43)	0.038*	0.85 (0.35–2.05)	0.719	0.80 (0.33–1.94)	0.621
Absence of preexisting AR	2.10 (1.18–3.68)	0.011	2.32 (1.05–5.11)	0.038	2.77 (1.13–6.77)	0.026
Hypertension	0.69 (0.34–1.42)	0.315	0.38 (0.15–0.97)	0.042*	0.38 (0.15–0.99)	0.047*
Previous PCI	0.87 (0.50–1.52)	0.869	0.45 (0.21–0.98)	0.045*	0.38 (0.17–0.85)	0.018*
Peripheral artery disease	0.33 (0.08–1.34)	0.120	0.50 (0.11–2.30)	0.376	0.44 (0.10–2.10)	0.297
LV dysfunction	1.57 (0.79–3.14)	0.198	1.20 (0.45–3.18)	0.712	1.0 (0.37–2.74)	0.991
Albumin (<3.5 g/L)	2.42 (0.96–6.11)	0.061	0.61 (0.13–2.91)	0.530	0.69 (0.14–3.42)	0.648
NT-proBNP, quartile 4 (pg/mL)	1.04 (0.51–2.10)	0.921	0.64 (0.27–1.53)	0.316	0.64 (0.27–1.54)	0.319
High-sensitivity troponin, quartile 4 (pg/mL)	1.42 (0.76–2.62)	0.269	1.74 (0.81–3.76)	0.159	1.51 (0.67–3.37)	0.321
Age ≥75 y	1.41 (0.51–3.897)	0.513			0.80 (0.18–3.66)	0.778
Male sex	0.93 (0.54–0.93)	0.808			0.56 (0.23–1.37)	0.202
BMI, quartile 4	0.70 (0.35–1.40)	0.314			0.82 (0.32–2.08)	0.669
Diabetes	0.92 (0.51–1.70)	0.792			1.24 (0.51–3.03)	0.638
Insulin therapy	1.03 (0.37–2.85)	0.960			1.18 (0.30–4.63)	0.811
NYHA III/IV	1.49 (0.73–3.10)	0.277				
STS score (≥4%)	1.34 (0.77–2.33)	0.301				
CAD	0.84 (0.48–1.48)	0.551				
Cerebrovascular arterial disease	1.21 (0.57–2.56)	0.622				
Previous stroke	1.55 (0.73–3.30)	0.252				
Previous MI	0.56 (0.22–1.41)	0.219				
Previous cardiac surgery	0.96 (0.35–2.67)	0.944				

BMI indicates body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HR, hazard ratio; LV, left ventricular; MI, myocardial infarction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; and TAVI, transcatheter aortic valve implantation.

* indicates statistical significance (P value<0.05).

body mass index showed no impact on 1-year survival based on multiple Cox regression analysis.

To evaluate whether circulating musclin improves risk estimation beyond conventional clinical risk scores based on its putative integration of untargeted health conditions as a remote biomarker, we stratified the patients into 4 groups based on their preprocedural circulating musclin levels and clinical risk (EuroSCORE II: low risk <4% versus intermediate risk ≥4%) to estimate joint effects for exploratory purposes: (1) higher musclin level (≥2.862 ng/mL) and low clinical risk (EuroSCORE II <4%); (2) higher musclin level (≥2.862 ng/mL) and intermediate EuroSCORE II; (3) lower musclin level (<2.862 ng/mL) and low EuroSCORE II; and (4) lower musclin level (<2.862 ng/mL) and intermediate EuroSCORE II. The Kaplan–Meier survival curves are shown in Figure – Panel D. Patients with AS undergoing TAVI showed numerically the highest survival rate, when high circulating musclin levels were observed in patients with low clinical risk (93.2%). However, lower circulating musclin levels in these patients allowed risk stratification into subgroups with numerically reduced 1-year survival rates (83.8%) (Figure – Panel D). Importantly, lower musclin levels in patients undergoing TAVI with intermediate risk based on EuroSCORE II resulted in even worse clinical outcome compared with an estimated intermediate clinical risk and higher musclin level (83.5% versus 71.5%) (Figure – Panel D).

However, because of the low number of patients at risk after stratification and the low number of events in this subgroup, statistical analysis did not achieve significance to firmly establish improved risk stratification, although log-rank for trend testing indicates differences for these 4 groups (P for trend=0.003).

DISCUSSION

While indications for TAVI have recently been expanded across the entire risk spectrum including patients with AS at low to intermediate clinical risk, appropriate TAVI risk stratification still needs improvement, especially in the expanded TAVI population at low to intermediate risk.[5,6,44] Therefore, we assessed the prognostic value of systemic musclin levels as a circulating biomarker in low- to intermediate-risk patients with AS undergoing TAVI and evaluated its performance of outcome prediction.

In this explorative pilot study, we found that lower circulating musclin levels in patients with AS at low to intermediate clinical risk are associated with a reduced 1-year survival after TAVI. In addition, low musclin levels in patients with AS were associated with a higher percentage of arterial hypertension, previous stroke, frailty, low albumin levels, and higher NT-proBNP levels, suggesting that this remote biomarker may integrate untargeted risk conditions by conventional clinical risk scores. In this study cohort, lower musclin levels also improved conventional clinical risk stratification by identifying patients with reduced 1-year survival after TAVI beyond EuroSCORE II. Experimental studies revealed that musclin acts as an exercise-responsive myokine that enhances physical endurance, while, in turn, musclin deficiency (with abolished systemic musclin levels) results in exercise intolerance.[9] Although our clinical study was not designed to examine direct effects of frailty or physical (in)activity on systemic musclin levels (or vice versa), lower musclin levels were associated with a higher prevalence of frailty, previous stroke, and lower albumin levels, indicating an integration of reduced physical health by systemic musclin levels. Notably, preclinical studies also revealed a cardioprotective role of circulating musclin. Transgenic overexpression or infusion of musclin following myocardial infarction or doxorubicin-induced cardiotoxicity resulted in improved survival and ameliorated myocardial hypertrophy by reducing cardiac inflammation and cardiomyocyte apoptosis in mice.[10,11] Interestingly, higher musclin levels were associated with reduced cardiac stress marker levels (NT-proBNP), lower frequency of atrial fibrillation, and arterial hypertension in our study cohort, suggesting an association of musclin with cardiac pathology. Together, these mechanistic studies suggest that reduced circulating musclin might indicate low physical activity, impaired exercise capacity, or frailty, which are all known drivers of adverse outcomes after TAVI, still insufficiently mapped by conventional clinical risk scores.[45–48] Indeed, patient populations undergoing TAVI are heterogeneous with regard to subclinical TAVI-specific risk factors (such as nutritional status[49] or physical impairments[28,29]) and circulating biomarkers (such as circulating musclin levels) may be more appropriate to integrate these TAVI-specific risk factors compared with restrictive definitions assessed by EuroSCORE II (eg, severe impairment of mobility), which will become even more important with the expansion of TAVI procedures in younger patients.

Most studies on circulating biomarkers were performed in patients undergoing TAVI at high clinical risk to identify those patients in whom the procedure can be futile. As patients at low to intermediate clinical risk have only recently been accepted as TAVI candidates, advanced risk assessment is needed to further improve patient selection and to enhance long-term outcome prediction in patients undergoing TAVI at low or intermediate clinical risk. Accordingly, our results provide support that circulating musclin levels in patients at low to intermediate risk may provide additional prognostic information compared with EuroSCORE II alone, helping to identify those patients with AS who had reduced 1-year survival after TAVI. Moreover, the late separation of survival curves by systemic musclin levels compared with the EuroSCORE II (which was developed to predict in-hospital or early mortality after cardiac surgery) may be attributed, at least in part, to lower exercise capacity before TAVI leading to an impaired or delayed physical and myocardial recovery postprocedurally, thereby translating into late survival effects. Estimation of later effects on survival by musclin, possibly by integrating TAVI-specific risk factors (not included in the current risk stratification), may become even more important with the expansion of TAVI procedures to younger patients, in whom early mortality (per se) is rather low. Notably, lower musclin levels in patients at low clinical risk were associated with reduced 1-year survival comparable to intermediate risk based on EuroSCORE II (and high musclin levels). Indeed, we further demonstrate that low systemic musclin levels in patients with increased clinical risk (intermediate risk based on EuroSCORE II) resulted in numerically even worse clinical outcome compared with intermediate clinical risk (and higher circulating musclin). Importantly, we did not observe major effects of diabetes, insulin treatment, or body mass index on circulating musclin levels or on survival based on univariate or multivariate analysis in our TAVI cohort, as musclin has been implicated as a putative target for obesity and associated diseases.[14,24]

Despite the relatively small number of patients, our TAVI cohort appears representative of the general

TAVI population, since the overall 1-year survival rate among patients undergoing TAVI in this study was 82%, which is similar to those reported by others.[4,50] Accordingly, besides circulating musclin, univariate predictors of adverse outcome in our study cohort were frailty,[28,29] COPD,[35] preprocedural absence of AR,[33,34] and EuroSCORE II,[8] which were also reported by previous studies. However, some limitations of our study need to be emphasized. First, this is an observational, single-center study with a limited number of patients undergoing TAVI who were at low to intermediate risk. Further prospective studies will be needed to validate the value of systemic musclin level in larger TAVI cohorts. Moreover, we had no validated information on the physical activity and muscle mass of the patients undergoing TAVI and patients were deemed to be frail based on clinical decision rather than validated scores, which both may have affected systemic musclin levels and prognostic outcome. To confirm the link between skeletal muscle, physical (in)activity or frailty, and systemic musclin level, further validation studies are needed that simultaneously measure circulating musclin, frailty with validated diagnostic tests, and muscle and bone mass, as well as function, in patients undergoing TAVI. Hence, we cannot directly confirm the integration of these untargeted health conditions by circulating musclin, although lower musclin levels were associated with catabolic surrogates or reduced physical capacity (such as frailty, history of stroke, or albumin levels) in our study cohort. Based on the results of this pilot study, it will be interesting to assess whether the myokine musclin, which is mainly expressed by skeletal muscle and bone, may be useful to identify patients with frailty or muscle wasting related to cardiovascular diseases and whether it may be of additional diagnostic value compared with rigorous frailty testing. As such, circulating musclin levels may provide a single quantitative biomarker reflecting the limitations of physical activity by the presence of severe AS preferentially in patients at intermediate risk for whom current risk prediction models provide insufficient information. As a cardioprotective and exercise-responsive myokine, systemic musclin levels may promote, at least in part, the beneficial impact of physical activity on cardiac remodeling. Hence, it will be interesting to discover whether exercise or stimulation of muscle contraction, which effectively increase circulating musclin in vivo, can reduce the clinical risk observed in our study.

CONCLUSIONS

Systemic musclin levels are associated with 1-year overall survival in patients undergoing TAVI who were at low to intermediate clinical risk. The prognostic value of baseline musclin levels should be validated in larger TAVI cohorts in order to support its role as a biomarker to be incorporated into risk stratification for patients with AS undergoing TAVI.

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